



xander Agudelo
Carlos A. Parra
Juan F. Acosta
Andrés Rincón
Aónica Guevara
Andrés Parra
aría C. Galarón
Mauricio Ávila
José J. Dangond
Gina Cáceres
Isabella Herrera
Zaava Ravid
Alejandro Moure
Miguel F. Porras
Catalina Amaya
Laura M. Escobar
Lorena Andrade
Sergio Arboleda
Catalina Jiménez
Daniela González
Maritza Sierra
Gina A. Árias
Guillermo Parra

Medellín
María C. Múnera
Eddie Manotas
Adrián Santamaria
Marilza P. Ruiz
Camilo A. Bernal

Barranquilla
Gina De Echeona

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: Expediente N° 13-101.248

Solicitud de Patente de Invención Titulada: "COMPOSICIÓN QUE
CONTIENE UN PROGESTÁGENO (DROSPIRENONA), UN
ESTRÓGENO (ETINILESTRADIOL) Y ÁCIDO TETRAHIDROFÓLICO"

Solicitante: BAYER SCHERING PHARMA AKTIENGESELLSCHAFT.

Nuestra Ref.: P2008/000245A

RECURSO DE REPOSICIÓN

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado como aparece al pie de mi firma, en mi condición de apoderado de la sociedad solicitante, y dentro del término legal previsto por el artículo 76 del código de Procedimiento Administrativo y de lo Contencioso Administrativo, me permito interponer RECURSO DE REPOSICIÓN en contra de la Resolución No. 61492, notificada por edicto desfijado el 21 de noviembre de 2014.

1. ANTECEDENTES

1.1 La solicitud de patente ventilada en este expediente fue presentada el 19 de abril de 2013, como divisional de la solicitud N° 09-000.752, con un Capítulo Reivindicatorio que constaba de 25 reivindicaciones.

1.2 La Superintendencia de Industria y Comercio (SIC) emitió la resolución No. 40558 notificado por fijación en la lista No. 028 del 16 de julio del 2013, objetando que ésta correspondía a una ampliación de la materia de la solicitud original

1.3. La Superintendencia de Industria y Comercio (SIC) emitió la resolución No. 73413 notificado por fijación en la lista No. 048 del 03 de diciembre del 2013, en donde la SIC resolvió revocar la decisión contenida en la Resolución No. 40558.

1.4. La Superintendencia de Industria y Comercio (SIC) emitió el primer examen de fondo notificado por fijación en la lista No. 017 del 29 de abril de 2014, correspondiente al oficio No. 4789, objetando la claridad y el nivel inventivo de la presente invención.

1.5. Mediante escrito radicado el 27 de agosto de 2014, respondí oportunamente el requerimiento formulado por la SIC, oportunidad en la que presenté un Capítulo Reivindicatorio Modificado con 17 reivindicaciones (junto con el recibo de pago correspondiente a 7 reivindicaciones adicionales), en donde proporcioné argumentos en favor de la claridad, y nivel inventivo.

1.6. La SIC por medio de la Resolución No. 61492, notificada por edicto desfijado el 21 de noviembre de 2014, niega las Reivindicaciones 1 a 17 por supuesta falta de nivel inventivo.

2. OBJETO DEL RECURSO

Que se revoque la resolución recurrida, y en su lugar se conceda el privilegio de patente de invención para las reivindicaciones contenidas en el **Capítulo Reivindicatorio Modificado adjunto** al presente Recurso de Reposición, o en su defecto aquellas reivindicaciones que el Despacho considere cumplen con los requisitos de patentabilidad.

3. FUNDAMENTO DEL RECURSO

Con referencia a los argumentos presentados por la SIC para desvirtuar el nivel inventivo de la presente solicitud en la resolución aquí recurrida, respetuosamente difiero del análisis expuesto, y procedo a refutar cada uno de dichos argumentos, exponiendo las motivaciones técnicas que desvirtúan la posición de ese Despacho.

3.1 En primer lugar, con el ánimo de brindar mayor claridad a la presente solicitud, me permito adjuntar un **Capítulo Reivindicatorio Modificado**, que reemplaza en su totalidad al Capítulo Reivindicatorio Modificado presentado el 27 de agosto de 2014 en respuesta al primer y único examen de fondo.

Así entonces, el Capítulo Reivindicatorio Modificado contiene los siguientes cambios:

- se incluyeron las nuevas Reivindicaciones 15 y 16 que corresponden a composiciones en donde se especifican los ingredientes y proporciones de los mismos, que encuentran soporte en los Ejemplos 5 y 6 del Capítulo Descriptivo; y en donde:
 - o La cantidad de 0.4-0.6 mg de tetrahidrofolato encuentra sustento en la reivindicación 39 de la solicitud parenteral en su versión originalmente presentada. El sustento para la cantidad de drospirenona y de etinilestradiol se encuentra en la reivindicación 38 de la solicitud parenteral;
 - o Las cantidades reivindicadas de lactosa monohidrato y MCC encuentran sustento en las reivindicaciones 40 y 41 de la solicitud parenteral;
 - o En estas dos nuevas reivindicaciones se especificaron las cantidades de hidroxipropilcelulosa (HPC), croscarmelosa sódica y esterato de magnesio;
 - o La cantidad reivindicada de HPC (0.8-2,4 mg) encuentra sustento en el segundo párrafo de la página 23 del Capítulo Descriptivo. Al respecto, cabe destacar que para una tableta de 80 mg, la cantidad preferida es de 1-3% HPC, lo cual corresponde a 0.8-2.4 mg;
 - o El sustento para la cantidad de croscarmelosa sódica (0.8 – 3.2 mg) se encuentra al final del primer párrafo de la página 25 del Capítulo Descriptivo. Al respecto, cabe destacar que para una tableta de 80 mg, la cantidad preferida de croscarmelosa sódica es de 1-4% HPC, lo cual corresponde a 0.8 – 3.2 mg;
 - o El sustento para la cantidad de estearato de magnesio (0.8 – 2.4 mg) se encuentra en el segundo párrafo de la página 24 del Capítulo Descriptivo. Al respecto, cabe destacar que para una tableta de 80 mg, la cantidad preferida de estearato de magnesio es de 1-3% HPC, lo cual corresponde a 0.8 – 2.4 mg.

Valga anotar que las modificaciones efectuadas al Capítulo Reivindicatorio cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial.

3.2 a- El Despacho señala que WO9953910 (D1) y US5916593 (D3) afectan el nivel inventivo de la presente invención sobre la Reivindicación 1 (y sus dependientes), así como la Reivindicación 15.

i) El Despacho argumenta que D1 da a conocer composiciones farmacéuticas que contienen ácido fólico junto con un anticonceptivo oral o una composición de reemplazo hormonal, así como la administración del ácido fólico y un sistema de administración de fármacos útiles para administrar composiciones farmacéuticas. D3 divulga un proceso de fabricación de unidades de dosificación farmacéutica que comprenden al menos desogestrel o Org 30659, presente en una cantidad de aproximadamente 0.005 a 1.0% en peso de cada unidad de dosificación, en donde el activo y los excipientes se mezclan con agua y se granulan.

La SIC presenta el siguiente cuadro comparativo entre las características esenciales de la presente invención frente a D1 y D3:

Tabla 1		
Características esenciales	D1	D3
Reiv 1		
Forma dosificación sólida	Forma dosificación sólida (resumen, Ej. 13 y reivindicaciones)	Forma dosificación sólida (Cols. 1 a 8)
Ácido 5-metil-(6S)-THF o su sal	Ácido fólico (resumen, Ej. 13 y reivindicaciones)	No menciona
Gránulos que contienen:	Tabletas que contienen:	Gránulos que contienen:
Drospirinona (Progestágeno) Celulosa microcristalina (relleno)	Progesterona (Progestágeno) (Pág. 9, líneas 29 a 31) Lactosa (relleno) (Pág. 16, líneas 1 a 9, resumen, Ejs. 1 a 13 y reivindicaciones)	Desogestrel (Progestágeno) (Col. 1, líneas 41 a 49) Celulosa microcristalina (relleno) (Col. 3, líneas 4 y 50)
Efecto: Anticonceptivo	Efecto: Anticonceptivo	Efecto: Anticonceptivo

A partir de su comparación, la SIC afirma que la diferencia entre la presente invención y D1 consiste en que la composición de la presente invención contiene celulosa microcristalina como agente de relleno, no obstante, no hay evidencia técnica que demuestre un efecto técnico diferente para la composición de la presente invención frente a la composición de D1.

Así, el problema técnico que resuelve la presente solicitud es “cómo modificar la dosificación sólida conocida en el documento D1 para proporcionar otra forma de dosificación sólida anticonceptiva alternativa”. Por lo tanto, en vista que D3 divulga una forma de dosificación sólida formada con gránulos que contienen desogestrel y celulosa microcristalina, la persona medianamente versada en la materia incluiría la celulosa microcristalina divulgada en D3 en la composición de D1, llegando a la presente invención de manera obvia.

El Despacho considera que lo divulgado en la Tabla 1, página 51, página 53 y el Ejemplo 5 no están asociados a alguna de las características técnicas reivindicadas, y que dichas condiciones y características allí divulgadas con conocidas por la persona medianamente versada en la materia

según Aulton¹. Adicionalmente, la SIC señala que el sustento del Ejemplo 1 es irrelevante ya que éste no tiene relación con la materia Reivindicada

ii) El Despacho agrega que la Reivindicación 15 (y su dependiente) carece de nivel inventivo en vista de la siguiente tabla comparativa.

Tabla 2

Características esenciales	D1	D3
Reiv 15		
Proceso	Composición	Proceso
Granular progestágeno y excipiente.	Progestágeno.	Granular progestágeno y excipiente.
Mezclar el ácido 5-metil-(6S)-THF.	Ácido Fólico	Mezclar .
Opcional: continuar.		Opcional: continuar.
Opcional: recolectarlos.	Excipiente. (resumen, Ejs. 1 a 13 y reivindicaciones)	Opcional: recolectarlos. (Todo el documento y reivindicaciones)

A partir de su análisis, la SIC afirma que la diferencia entre la presente invención y D3 consiste en que el procedimiento de D3 menciona expresamente la mezcla del granulado con el derivado de ácido fólico, no obstante, no hay evidencia técnica que demuestre un efecto técnico diferente para la composición de la presente invención frente a la composición de D1.

Así, el problema técnico que resuelve la presente solicitud es “*cómo modificar el proceso conocido en D1 para proporcionar otro proceso alternativo*”. Sin embargo, el hecho de que D1 dé a conocer composiciones farmacéuticas que contienen ácido fólico junto con un anticonceptivo oral o una composición de reemplazo hormonal motivaría a una persona medianamente versada en la materia a incluir el derivado de ácido fólico en el método de D1, obteniendo el procedimiento de la Reivindicación 15, por lo cual la presente invención se considera obvia.

iii) Frente a mis argumentos presentados en mi respuesta al primer y único examen de fondo, la SIC concluye que: Los resultados de los Ejemplos 5 y 6 no son sorprendentes ya que el texto Remington afirma que la disolución de una tableta depende no del método de granulación sino de sus características, por lo que no se puede atribuir el método de compresión a los efectos de disolución.

b- i) En primer lugar, me permito aclarar que el Capítulo Reivindicatorio Modificado adjunto reclama clara y específicamente una forma de dosificación unitaria, oral y sólida caracterizada porque comprende i) ácido 5-metil-(6S)-tetrahidrofólico o una de sus sales

¹ Michael E Aulton, *Pharmaceutics: The Science of Dosage Form Design* (Edinburgh ; New York: Churchill Livingstone, 2002), página 109.

aceptables desde el punto de vista farmacéutico; y ii) gránulos que comprenden drospirenona y celulosa microcristalina.

Ahora bien, estoy de acuerdo con el Despacho en que el documento D1 (WO9953910) debe ser considerado el arte previo más cercano (aun teniendo en cuenta las modificaciones realizadas en el Capítulo Reivindicatorio Modificado adjunto), debido a que D1 divulga anticonceptivos orales que comprenden un componente de ácido fólico. La diferencia entre D1 y la presente invención radica fundamentalmente en el uso de gránulos que comprenden celulosa microcristalina (MCC) en presencia de ácido 5-metil-(6S)-tetrahidrofólico (un derivado del ácido fólico que no se encuentra divulgado en D1 y que es particularmente sensible a la humedad).

En la Resolución 61492, la SIC afirma que el uso de MCC es la única diferencia entre D1 y la invención reclamada en la Reivindicación 1 actual de la presente invención. Respetuosamente, me permito señalar que esta afirmación es incorrecta en tanto que D1 no enseña la presencia de gránulos ni del ácido tetrahidrofólico particularmente sensible a la humedad. De hecho, D1 tampoco menciona a la drospirenona.

En atención a ello, cabe resaltar que el problema que pretende resolver la presente invención es el de proporcionar una forma de dosificación anticonceptiva en la cual el ácido 5-metil-(6S)-tetrahidrofólico sea suficientemente estable, y el progestágeno, es decir la drospirenona, sea liberado de manera suficientemente rápida.

La SIC ha definido un problema diferente, particularmente: *“la modificación de la forma de dosificación sólida conocida del documento D1 con el fin de proporcionar otra forma de dosificación sólida anticonceptiva alternativa”*.

Al respecto, cabe aclarar que la presente invención resuelve los dos problemas planteados más arriba de manera sorprendente e impredecible a la luz de lo divulgado en D3.

Por consiguiente, y en vista de las enseñanzas de D1, el inventor de la presente invención se enfrentó al desafío de proporcionar una composición alternativa que presente una liberación rápida de la drospirenona y al mismo tiempo mantenga la estabilidad del folato (que es sensible a la humedad) en la composición final.

En este sentido, es pertinente señalar que D1 no hace referencia alguna al desafío planteado en el párrafo anterior. Además, desde un principio, la persona medianamente versada en la materia no habría considerado someter la formulación de la presente invención a una granulación húmeda

debido a la inestabilidad conocida del ácido 5-metil-(6S)-tetrahidrofólico. Éste fue precisamente el motivo por el cual el inventor de la presente invención empleó la compresión directa en sus primeros intentos de formular una forma de dosificación que proporcione una liberación rápida de la drospirenona. Sin embargo, tal como se muestra en los Ejemplos 1 a 4 de la presente solicitud, estas formulaciones elaboradas por compresión directa **no** exhibieron una liberación suficientemente rápida de la drospirenona.

A fin de sustentar mis argumentos, me permito hacer referencia a las enseñanzas y a los datos exhibidos en el libro de Remington que demuestran que al cambiar de una compresión directa a una granulación es de esperar que se produzca una disminución en la velocidad de disolución (véase la página 549, Figura 31-9, Edición 18; esta página se adjuntó en mi respuesta al primer y único examen de fondo, presentado el 27 de agosto de 2014). Lieberman y colaboradores (Pharmaceutical Dosage Forms: Tablets) proporcionan una enseñanza similar en relación con la MCC (véase el párrafo de la página 175 que se refiere al producto "Avicel"; esta página se adjuntó en mi respuesta al primer y único examen de fondo, presentado el 27 de agosto de 2014) cuando manifiestan lo siguiente:

"Cuando se granula en húmedo, se seca y se comprime, ésta (MCC) no se desintegra tan fácilmente como cuando se la utiliza en seco. Puede ser empleada con casi todos los fármacos excepto con aquéllos que son sensibles a la humedad (tales como la aspirina, la penicilina, las vitaminas), a menos que sea sometida a un secado hasta alcanzar un contenido de agua inferior al 1% y luego sea manufacturada en un área deshumedecida". (subrayado fuera de texto)

Teniendo en cuenta lo anterior, dado que en la compresión directa la MCC no está húmeda, cabe concluir que el arte previo citado **no** sugiere el uso de MCC y granulación húmeda una vez que la persona medianamente versada en la materia comprobó que la compresión directa es inefectiva en lo que respecta a proporcionar una liberación rápida. Por el contrario, tanto Remington como Liebermann *et al.* argumentan en contra de tal uso, pues indican que la MCC húmeda no se desintegra tan bien como cuando se encuentra seca.

Asimismo, Liebermann *et al.* enseña claramente que la MCC no debe ser empleada junto con fármacos sensibles a la humedad (véase más arriba). El ácido 5-metil-(6S)-tetrahidrofólico es precisamente uno de tales fármacos sensibles a la humedad.

Por consiguiente, el presente inventor tuvo que enfrentarse al prejuicio de que el ácido tetrahidrofólico no sería estable en condiciones de granulación y no sería compatible con el uso de MCC húmeda (véase el texto de Lieberman *et al.* discutido más arriba).

Por tal motivo, fue altamente sorprendente descubrir que las composiciones que se reivindican en la presente invención exhiben tanto una velocidad de liberación satisfactoria del progestágeno como una estabilidad suficiente del folato, tal como se demuestra en los Ejemplos 5 y 6 del Capítulo Descriptivo.

De otra parte, en la Resolución 61492, el Despacho señala que D3 divulga el uso de MCC en formas de dosificación anticonceptivas, y con base en ello concluye que la solución que ofrece la presente invención resulta obvia a la luz de lo divulgado en D1 y D3. Respetuosamente discrepo del punto de vista de la SIC.

En primer lugar, D3 no describe el uso de MCC en alguna de las formas de dosificación ejemplificadas (véanse los ejemplos I-XI), sino que menciona en forma general que la MCC es un desintegrante útil. En segundo lugar, el inventor en D3 no tuvo que enfrentarse a los problemas de los folatos sensibles a la humedad, los cuales son considerados incompatibles con la MCC húmeda en un proceso de granulación.

La SIC señala tres (3) efectos que se desprenden de los ejemplos de realización de la presente solicitud y concluye que estos resultados o efectos no están asociados a alguna de las características técnicas de la composición farmacéutica reivindicada. En vista de lo reclamado en la Reivindicación 1 actual, respetuosamente difiero del punto de vista del Despacho

En particular, en el punto (1), la SIC señala que el folato es más estable en un envase cerrado que en un envase abierto a temperaturas mayores. Al respecto, cabe destacar que la comparación de la estabilidad en condiciones diferentes carece de relevancia. Lo importante en este caso es que en todos los Ejemplos 1 a 6 se obtiene una estabilidad satisfactoria (es decir, suficiente) del folato. Esto probablemente no sea sorprendente en el caso de los ejemplos de compresión directa (Ejemplos 1 a 4), pero es totalmente inesperado y sorprendente en el caso de las composiciones granuladas que contienen MCC de los ejemplos 5 y 6.

Respecto del punto (2), coincido con la opinión de la SIC en que la liberación del EE y el THF es inmediata, mientras que la drospirenona se libera en forma lenta e insatisfactoria cuando se emplea la compresión directa (Ejemplos 1 a 4), pero se libera suficientemente rápido al emplear la granulación (Ejemplos 5 y 6).

En cuanto al punto (3), cabe señalar que todos los ejemplos, con excepción del Ejemplo 3, comprenden croscarmelosa sódica. Si bien es correcto que se agrega mayor cantidad de croscarmelosa en el Ejemplo 5 que, por ejemplo, en el Ejemplo 4, también es preciso resaltar que en el Ejemplo 6 se emplea la misma cantidad de croscarmelosa sódica que en el Ejemplo 4. Ambos Ejemplos 5 y 6 muestran una liberación suficientemente rápida de la drospirenona, por lo que la croscarmelosa sódica no es el factor que incrementa la disolución de la drospirenona. Son los gránulos que comprenden drospirenona y MCC los que producen este efecto.

Finalmente, cabe reiterar que los problemas combinados que se discutieron más arriba (es decir, el problema de lograr una liberación rápida de la drospirenona y el de mantener simultáneamente la estabilidad del ácido 5-metil-(6S)-tetrahidrofólico) no se pueden resolver en forma aislada, pues es esperable que el empleo de la granulación para resolver el problema de la liberación rápida afecte directamente al otro problema, es decir, la estabilidad del ácido tetrahidrofólico. El inventor tuvo que resolver estos dos problemas interrelacionados en forma simultánea. Cabe destacar que es muy usual en algunas de las jurisdicciones de referencia, incluyendo Europa, que un problema no pueda ser separado en dos problemas parciales, en particular, si es esperable que la solución a uno de los problemas afecte el resultado con respecto al otro problema. Por lo tanto, la solución que propone el presente inventor a los dos problemas planteados habría sido percibida como “*incompatible*” por la persona medianamente versada en la materia al momento en que se presentó la solicitud prioritaria correspondiente a la presente solicitud en estudio. Es decir, no habría habido expectativa razonable alguna de éxito.

Con base en lo anteriormente expuesto, cabe concluir que la solución a los problemas planteados en la presente solicitud no era obvia al momento en que se presentó la solicitud prioritaria correspondiente a la presente solicitud en estudio, en particular, si dicha solución no se analiza en forma aislada y se resuelve en conjunto tal como se describe en el caso de la presente solicitud de patente. Por consiguiente, el objeto de las presentes reivindicaciones reviste nivel inventivo.

A fin de confirmar los argumentos expuestos, se adjunta la Declaración firmada de la inventora Dra. Kristina King (Anexo 2). Esta declaración también fue presentada en relación con la solicitud parenteral. De la Declaración adjunta se desprende que aún si el tetrahidrofolato es agregado en una etapa tardía de la granulación, la MCC ha absorbido humedad durante la granulación y es esperable que la MCC húmeda afecte negativamente la estabilidad del folato.

En lo que respecta a las reivindicaciones dirigidas a un procedimiento de fabricación (Reivindicaciones 17 y 18), cabe destacar que estas reivindicaciones incluyen las mismas características de granulación, MCC y ácido 5-metil-(6S)-tetrahidrofólico, por lo que son inventivas en base a los mismos conceptos que los productos resultantes.

En la Resolución 61492, la SIC menciona que la característica relacionada con la MCC fue mencionada en la solicitud parenteral y en una reivindicación independiente, y resalta que esta reivindicación fue rechazada, lo cual confirmaría la ausencia de nivel inventivo. Al respecto, me permito hacer hincapié en el hecho de que el destino de la solicitud parenteral no ha sido decidido aún, pues esta solicitud se encuentra actualmente bajo revisión judicial. Por consiguiente, aún no existe un pronunciamiento final respecto de la patentabilidad y nivel inventivo del objeto reclamado en dicha solicitud parenteral.

ii) Ahora bien, en la página 9 de la Resolución 61492, el Despacho se refiere a mis argumentos presentados en la respuesta del 27 de agosto de 2014. En particular, la SIC señala que “el texto de Remington dice en realidad que la disolución de la tableta depende de sus características y no del método de granulación per se, de modo que no puede afirmarse que la compresión directa sea inefectiva para proporcionar disolución rápida”.

Al respecto, en respuesta a este comentario realizado por la SIC, cabe destacar que Remington afirma que el método de granulación no es el factor principal, y el inventor de la invención ha demostrado claramente y en todo momento que, para el caso de la presente formulación, lo importante es el uso de la granulación y de la MCC, véanse los Ejemplos 1-4 versus los Ejemplos 5-6 de la presente solicitud. La drospirenona no tiene una disolución rápida y suficiente aún si se emplea, por ejemplo, croscarmelosa en la compresión directa (véase el Ejemplo 4 del Capítulo Descriptivo).

Finalmente, la SIC señala que la MCC puede ser empleada como materia prima deshidratada a fin de evitar problemas con los excipientes húmedos y los fármacos sensibles a la humedad (en el presente caso, el tetrahidrofolato). En respuesta a este comentario realizado por la SIC, me permito afirmar que esto puede ser cierto, pero tal como se explica en la Declaración del inventor adjunta, la MCC absorbe la humedad durante la formación del gránulo, por lo que se esperaría que para la presente invención se produzca el problema de la sensibilidad a la humedad. Sin embargo, el resultado obtenido fue totalmente sorprendente, pues este problema no surgió.

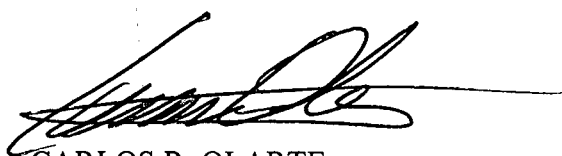
En atención a lo expuesto, me permito aclarar que los comentarios adicionales que hace la SIC en la anteúltima página de la Resolución Denegatoria no desvirtúan el nivel inventivo del objeto reclamado en la presente solicitud.

4. Para terminar, de conformidad con lo establecido en el artículo 59 del Código Contencioso Administrativo, solicito respetuosamente que todos y cada uno de los puntos planteados en el presente recurso sean resueltos de manera individual, completa y motivada, respecto de las razones de hecho, derecho y/o conveniencia que lleven a esa Superintendencia a adoptar la decisión que estime frente a la solicitud aquí formulada.

5. NOTIFICACIÓN

Recibiré notificaciones en mis oficinas ubicadas en la Carrera 5 No. 34-03, de Bogotá.

Atentamente,



CARLOS R. OLARTE

C.C. No. 79.782.747 de Bogotá

T.P. 74.295

Anexos:

- Capítulo Reivindicatorio Modificado;
- Anexo 2: Declaración firmada de la inventora Dra. Kristina King
- Anexo 3: Traducción de la declaración firmada de la inventora Dra. Kristina King
- Anexo 4: Swarbrick *et al.* (Documento citado dentro de la declaración firmada de la inventora Dra. Kristina King)
- Recibo de pago por 8 reivindicaciones adicionales.
- Recibo de pago correspondiente a la tasa de modificación de las reivindicaciones.

CAPÍTULO REIVINDICATORIO MODIFICADO
(Recurso de Reposición)

1. Una forma de dosificación unitaria, oral y sólida caracterizada porque comprende
 - i) ácido 5-metil-(6S)-tetrahidrofólico o una de sus sales aceptables desde el punto de vista farmacéutico; y
 - ii) gránulos que comprenden drospirenona y celulosa microcristalina.
2. La forma de dosificación de acuerdo con la Reivindicación 1, caracterizada porque comprende un estrógeno.
3. La forma de dosificación de acuerdo con la Reivindicación 2, caracterizada porque el estrógeno se selecciona del grupo formado por etinilestradiol, estradiol, sulfamatos de estradiol, valerato de estradiol, benzoato de estradiol, estrona, mestranol y sulfato de estrona.
4. La forma de dosificación de acuerdo con la Reivindicación 3, caracterizada porque el estrógeno es etinilestradiol.
5. La forma de dosificación de acuerdo con cualquiera de las reivindicaciones precedentes, caracterizada porque la drospirenona se encuentra en forma micronizada.
6. La forma de dosificación de acuerdo con cualquiera de las reivindicaciones precedentes, caracterizada porque el ácido tetrahidrofólico es una sal del ácido 5-metil-(6S)-tetrahidrofólico aceptable desde el punto de vista farmacéutico.
7. La forma de dosificación de acuerdo con la Reivindicación 6, caracterizada porque la sal del ácido 5-metil-(6S)-tetrahidrofólico es la sal de calcio.
8. La forma de dosificación de acuerdo con la Reivindicación 7, caracterizada porque la sal de calcio del ácido 5-metil-(6S)-tetrahidrofólico se encuentra en forma cristalina.
9. La forma de dosificación de acuerdo con la Reivindicación 8, caracterizada porque la forma cristalina es la forma cristalina Tipo I.

10. La forma de dosificación oral y sólida de acuerdo con la Reivindicación 1, caracterizada porque la unidad de dosificación oral y sólida está en forma de comprimido, cápsula o sachet.
11. La forma de dosificación oral y sólida de acuerdo con la Reivindicación 10, caracterizada porque la unidad de dosificación oral y sólida está en forma de comprimido.
12. La forma de dosificación oral y sólida de acuerdo con cualquiera de las Reivindicaciones 1 a 11, caracterizada porque comprende entre 2 y 4 mg de drospirenona.
13. La forma de dosificación oral y sólida de acuerdo con cualquiera de las Reivindicaciones 2 a 11, caracterizada porque comprende una cantidad de estrógeno correspondiente a una cantidad terapéuticamente equivalente de etinilestradiol de 0,01 a 0,05 mg.
14. La forma de dosificación oral y sólida de acuerdo con cualquiera de las Reivindicaciones 2 a 13, caracterizada porque comprende 2-4 mg de drospirenona y 0.01 a 0.05 mg de etinilestradiol.
15. La forma de dosificación oral y sólida de acuerdo con cualquiera de las reivindicaciones 2 a 14, caracterizada porque comprende
 - i) gránulos que comprenden
 - a) de 2.5 a 3.5 mg de drospirenona,
 - b) de 0.02 a 0.03 mg de etinilestradiol,
 - c) de 15 a 35 mg de celulosa microcristalina,
 - d) de 30 a 55 mg de lactosa monohidrato, y
 - e) de 0.8 a 2.4 mg de hidroxipropilcelulosa,
 - ii) de 0.4 a 0.6 mg de la sal de calcio del ácido 5-metil-(6S)-tetrahidrofólico,
 - iii) de 0.8 a 3.2 mg de croscarmelosa sódica, y
 - iv) de 0.8 a 2.4 mg de estearato de magnesio.
16. La forma de dosificación oral y sólida de acuerdo con cualquiera de las Reivindicaciones 2 a 14, caracterizada porque comprende
 - i) gránulos que comprenden

- a) de 2.5 a 3.5 mg de drospirenona,
- b) de 0.02 a 0.03 mg de etinilestradiol,
- c) de 40 a 80 mg de celulosa microcristalina, y
- d) de 0.8 a 2.4 mg de hidroxipropilcelulosa,
- ii) de 0.4 a 0.6 mg de una sal de calcio del ácido 5-metil-(6S)-tetrahidrofólico,
- iii) de 0.8 a 3.2 mg de croscarmelosa sódica, y
- iv) de 0.8 a 2.4 mg de estearato de magnesio.

17. Un proceso para la fabricación de una forma de dosificación de acuerdo con cualquiera de las Reivindicaciones 1 a 16, caracterizado porque comprende los pasos de:

- (i) someter la drospirenona y la celulosa microcristalina a un proceso de granulación,
- (ii) mezclar el ácido 5-metil-6(S)-tetrahidrofólico o una de sus sales con los gránulos formados en el paso (i), y
- (iii) opcionalmente continuar con el proceso de granulación, y/o
- (iv) opcionalmente recolectar los gránulos,
- (v) formular los gránulos obtenidos en formas de dosificación unitarias, orales y sólidas.

18. El proceso de acuerdo con la Reivindicación 17, caracterizado porque el paso de granulación se lleva a cabo mediante granulación en lecho fluido.

INVENTOR STATEMENT

Dear Sirs,

The solution of the described problem has to be evaluated as combined solution, it cannot be divided into two isolated tasks.

The task was to provide a formulation out of which DRSP dissolves quickly and in which Metafolin (calcium salt 5-methyl-(6S)-tetrahydrofolic acid) is stable. This combination is the specific problem since, the measures to increase the dissolution (fluidized bed granulation) lead to an decreased Metafolin stability (heat and humidity access), therefore it was novel and surprising to find formulation and manufacturing for a DRSP / Metafolin formulation solving both problems.

The mentioned handbook passage (Swarbrick) related to the granulation process is very generic ("tends to enhance") and not an instruction for the solution of this specific task.

Several studies have demonstrated that the granulation process, in general, enhances the dissolution rate of poorly soluble drugs (1). The use of diluents and fillers such as starch (2), anhydrous (3) and spray dried lactose (4,5), microcrystalline cellulose (6), and compression force, particle size and lubricants (7) tends to enhance the hydrophilicity of the active ingredients and improve their dissolution characteristics. In this regard, the wet granulation procedure was considered a superior method compared to other methods. However, newer tableting machines and excipients, accompanied by careful formulation and proper mixing sequence, will permit preparation of tablets with good dissolution characteristics and not dictated by the method of preparation per se.

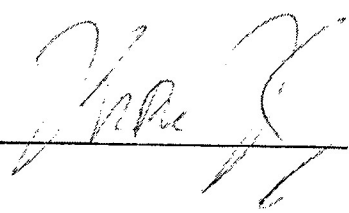
In addition the usage of Avicel/MCC to solve the dissolution and stability problem is something, which an expert would not do, since it is known, that the disintegration is negatively influenced, which affects the dissolution negatively, and the excipient is not recommended for moisture-sensitive drugs, like Metafolin is. The developed formulation has a moisture content above 1%, which is expected to be a humidity, which is not feasible for a MCC formulation containing a moisture-sensitive drug (cf. Liebermann).

Avicel (microcrystalline cellulose) is a highly effective disintegrant. It has a fast wicking rate for water, hence, it and starch make an excellent combination for effective and rapid disintegration in tablet formulations. One drawback to its use is its tendency to develop static charges with increased moisture content, sometimes causing striation or separation in the granulation. This can be partially overcome by drying the cellulose to remove the moisture. When wet-granulated, dried, and compressed, it does not disintegrate as readily as when unwetted. It can be used with almost all drugs except those that are moisture-sensitive (such as aspirin, penicillin, and vitamins) unless it is dried to a moisture content of less than 1% and then handled in a dehumidified area.

Therefore the solution of both problems is not covered by the mentioned literature.

Best regards

2013-10-09

A handwritten signature in dark ink, appearing to read 'Kristina King', written over a horizontal line.

Dr. Kristina King
Bayer Pharma AG
Head In-licensing Opportunities
Global Drug Discovery - External Technology & Innovation
13353 Berlin, M001, 05, 538

DECLARACIÓN DEL INVENTOR

Estimados señores,

La solución al problema planteado debe ser evaluada como una solución combinada, no puede ser dividida en dos tareas aisladas.

La tarea era la de proporcionar una formulación a partir de la cual la drospirenona (DRSP) se disuelva rápidamente y en la cual el Metafolin (la sal de calcio del ácido 5-metil-(6S)-tetrahidrofólico) sea estable. Esta combinación constituye el problema específico, pues las medidas para incrementar la disolución (granulación en lecho fluido) producen una disminución de la estabilidad del Metafolin (acceso a la humedad y al calor). Por consiguiente, fue novedoso y sorprendente encontrar una formulación y un proceso de manufacturación para una formulación de DRS/Metafolin que resuelva ambos problemas.

El párrafo del mencionado libro de textos (Swarbrick) que se refiere al proceso de granulación es muy general ("tiende a aumentar") y no es una instrucción para resolver esta tarea específica.

"Diversos estudios han demostrado que el proceso de granulación, en general, aumenta la velocidad de disolución de fármacos poco solubles (1). El uso de diluyentes y materiales de relleno tales como almidón (2), lactosa anhidra (3) y lactosa pulverizada (4,5), celulosa microcristalina (6), y fuerza de compresión, tamaño de partícula y lubricantes (7) tiende a aumentar la hidrofilia de los ingredientes activos y mejorar las características de disolución de los mismos. Al respecto, cabe destacar que el proceso de granulación húmeda fue considerado superior en comparación con otros métodos. Sin embargo, las máquinas más nuevas para producción de tabletas y los excipientes más nuevos, si están acompañados de una formulación cuidadosa y una secuencia de mezclado adecuada, permitirán la preparación de tabletas con buenas características de disolución que no estarán regidas por el método de preparación en sí."

Asimismo, el experto no emplearía Avicel/MCC con el fin de resolver el problema de disolución y estabilidad, pues es sabido que se ejerce una influencia negativa sobre la desintegración, lo cual afecta negativamente la disolución, y el excipiente no está recomendado para los fármacos sensibles a la humedad tales como el Metafolin. La formulación desarrollada tiene un contenido de humedad mayor que el 1%, lo cual puede ser calificado como humedad y no es viable para una formulación de MCC que contiene un fármaco sensible a la humedad (véase el texto de Liebermann que se indica a continuación).

Avicel (celulosa microcristalina) es un desintegrante muy efectivo. Tiene una velocidad rápida de absorción para el agua. Por consiguiente Avicel y almidón forman una combinación excelente para una desintegración rápida y efectiva en

formulaciones de tabletas. Un inconveniente para su uso es su tendencia a desarrollar cargas estáticas a mayor contenido de humedad, causando a veces estrías o separación en la granulación. Esto puede ser parcialmente superado por medio del secado de la celulosa a fin de remover la humedad. Cuando se granula en húmedo, se seca y se comprime, ésta no se desintegra tan fácilmente como cuando se la utiliza en seco. Puede ser empleada con casi todos los fármacos excepto con aquéllos que son sensibles a la humedad (tales como la aspirina, la penicilina, las vitaminas), a menos que sea sometida a un secado hasta alcanzar un contenido de agua inferior al 1% y luego sea manufacturada en un área deshumedecida”.

Por consiguiente, la solución a ambos problemas no está abarcada por la literatura mencionada.

Atentamente,

Dr. Kristina King

Bayer Pharma AG

Jefa del área que ofrece oportunidades para adquirir licencias

Global Drug Discovery – External Technology & Innovation

13353 Berlin, M001, 05, 538

required amount of liquid binder based on the formulation composition. However, this is a challenging task, since the liquid binder required for high-shear granulation depends on a number of formulation and process factors, such as physicochemical properties of the starting materials (API and excipients), type of the binder used, impeller speed, wet-massing time, etc.

5. FACTORS AFFECTING THE GRANULATION PROCESS AND GRANULE PROPERTIES

Performance and physical properties of the compressed tablets are driven by properties of the granules. Yajima et al. (19) examined the relationship between particle size distribution and physical properties of the obtained granules (e.g., angle of repose, angle of spatula, loose bulk density, tapped bulk density, compressibility) and the resulting tablets (hardness and weight variation of tablets). The particle size distribution of the granules used for tablet compression was expressed as a function of median particle size, and standard deviation with a logarithmic normal distribution. Physical properties of granules and the compressed tablets were significantly affected by this factor. Tablet hardness increased as the median particle size decreased, when the standard deviation was <1.0 .

In another example, Wikberg et al. (20) produced 11 granulations of a common filler (lactose) and three granulations of a high-dose drug (dipentum) by wet granulation with polyvinylpyrrolidone (PVP) as binder, in a high-shear mixer granulator. The agglomeration process was varied to produce granules with varying granule porosity. The granule fragmentation during compression was evaluated by measurements of air permeability of the tablets. The results showed that the degree of granule fragmentation during compression was related to the granule porosity before compaction. A granulation with a higher porosity had a higher fragmentation propensity during compression. The tablet strength correlated well with the degree of fragmentation, i.e., a granulation with a higher degree of fragmentation yielded tablets of a higher hardness. Variations in compactibility can be explained by variations in granule porosity for the same formulation that was wet granulated under different process conditions. Therefore, the formulation variables and granulation process should be controlled to produce granules with the desired properties. Since granule formation in high-shear wet granulation is dependent on the degree of liquid saturation, the factors that influence the degree of liquid saturation should be optimized to obtain an optimal granulation formulation. The factors that affect the degree of liquid saturation (which depends on the amount of liquid added as well as on the densification of the granules) are formulation, process, and apparatus variables. Hence, the granulation process and the properties of the granules are affected by the aforementioned variables.

5.1. Formulation Variables

Besides the API, excipients such as a filler or fillers, a disintegrant (not applicable to controlled release), and a binder are also included in the powder mixture of a tablet formulation. The fillers used in tablet formulations can be classified into two categories, based on their water solubility: soluble fillers such as lactose, sucrose, mannitol, etc., and insoluble fillers such as MCC, starch, calcium carbonate, calcium phosphate, etc. The binders used in the wet granulation process are water-soluble

polymers such as gelatin, PVP, HPMC and sugars such as glucose, sucrose, and sorbitol. Some of the commonly used disintegrants are sodium starch glycolate, cross-linked PVP, and cross-linked sodium carboxymethylcellulose. These excipients are available in various grades from vendors. Hence, the physical properties such as particle size distribution, particle shape, surface morphology, surface area, and solubility of API and excipients in the binder solution could vary considerably. The rate and the final degree of densification are controlled by the physical properties such as particle size distribution, particle shape, surface morphology, surface area, solubility in the binder solution, etc., of the starting materials. Therefore, the physical characteristics of drug and drug loading, the types and amount of excipients, and the type and amount of binder used could affect the rate and the final degree of densification of the resulting granules. Moreover, these aspects of the powder mixture can also affect the amount of liquid required for granulation and the degree of liquid saturation in the agglomerates, during the wet-granulation process, which in turn affect the physical properties of the obtained granules.

5.2. Effects of Starting Materials

The physical properties of the granules are influenced by the physical properties of the starting materials. For example, the shape, size, and size distribution of the particles of the starting materials can affect the packing pattern of a powder mixture, and ultimately the final degree of densification and the strength of the resulting granules. The extent of granule densification affects the degree of liquid saturation of the powder mixture, and the amount of liquid binder required for granulation. The total surface area of the starting materials, related to the particle size and porosity of the starting materials, will affect the amount of liquid binder required for granulation. The liquid adsorption of the starting material could also affect the amount of liquid binder required for wet granulation. Therefore, the amount of binder solution required for granulation depends on the formulation composition, and the physical characteristics of the starting materials. In a study by Schaefer et al. (21), when the mean particle size of lactose was decreased, the amount of liquid required for granulation was increased to obtain a similar particle size of granules in high-shear granulation.

The influence of the primary particle size of DCP on granule growth in a Lödige MSGR high-shear mixer granulator was investigated by Schaefer et al. (22). Two batches of DCP, one with a narrower particle distribution and smaller geometric mean diameter, and the other with a wider particle size distribution and a larger geometric mean diameter were used. The batch with the narrower particle size distribution and smaller geometric mean diameter was more easily densified than the one with the wider particle size distribution and a larger geometric mean diameter, because it was overwetted at lower moisture content. The granules with wider particle size distribution were produced from the DCP with a wider particle size distribution and larger geometric mean diameter.

The strength of wet agglomerates can be dominantly affected by the degree of liquid saturation and the primary particle size of the starting materials. Consequently, the growth mechanism and drug content uniformity of the resulting granules can be affected.

The influence of the primary particle size of lactose on the breakage of erythro-sine granules was investigated by van den Dries et al. (4). The results showed that a decrease in particle size of the starting material, lactose, led to a decrease in

f82

breakage of granules. When granule breakage was absent, the granules remained intact and the preferential layering of the smallest particles yielded inhomogeneous granules.

The effect of particle size of the lactose on the homogeneity of low-dose steroid hormone distribution in granules produced in high-speed mixers was studied by Vromans et al. (23). When a micronized low-dose steroid hormone was granulated with unmiconized lactose at 250 rpm, inhomogeneity of active was observed. The coarse particle size fractions of the granules were found to be superpotent, up to 150% of the mean drug content, whereas the fine size fraction showed a corresponding subpotency of 50%. However, when the particle size of lactose was reduced, a better drug distribution was seen. This was attributed to an increase in the tensile strength of the nuclei due to the smaller particle size of lactose.

The effect of particle size of lactose on the homogeneity of estradiol granules prepared in a 10 L high-shear mixer was studied by van den Dries et al. (15). Three different particle sizes of lactose were granulated with 0.1% micronized estradiol (5 μ m) using an aqueous solution of hydroxypropyl cellulose (HPC) as a binder. Granules prepared with the largest lactose particles (141 μ m) yielded a homogenous granulate. However, after a prolonged processing time, demixing was observed. Contrary to the largest particles, granulation with the smaller lactose particles (23 and 50 μ m) led to demixing in the first minute, although to a lesser extent. It was concluded that granulation with the largest particles resulted in breakage of the granules, thereby preventing demixing. However, once the granules were strong enough (smaller particle size and prolonged process time) to survive the shear forces, demixing was observed. The extent of demixing depended on the particle size difference.

The size distribution of granules prepared from three different tablet excipients, lactose, glucose, and mannitol, in a high-shear granulator, were studied by both sieve analysis and laser light diffractometry (24). Both the shapes and the size distribution of the granules produced from the three excipients differed.

The crystallinity of the starting materials affected the granulation process and the properties of the granules. The effect of crystallinity of MCC on wet granulation, in binary mixtures of MCC and corn starch (CS), was investigated by Suzuki et al. (25). The crystallinity of MCC was modified, producing amorphous material by milling in a jet mill (J-MCC) and a vibrational rod mill (R-MCC). Crystallinity of J-MCC was nearly equal to that of intact MCC (I-MCC), but that of R-MCC was remarkably low due to the mechano-chemical effect. The growth rate of granules with R-MCC was greater than that with I-MCC and J-MCC. The formulations containing I-MCC and J-MCC produced granules with a core (MCC and CS) around which CS was layered. R-MCC provided granules in which CS and abraded MCC were homogeneously mixed. In addition, R-MCC remarkably decreased the difference in drug content among the size fractions of granules compared with I-MCC. The decrease in crystallinity of MCC increased the abrasion of the material by the impeller. This resulted in a greater growth rate of granulation.

The physical properties of the API also affect the wet granulation process and the properties of the resulting granules. For example, when the particle shape of the API was changed from spherical to plate like due to a change in the crystallization solvent, the compressibility of the resulting granules dramatically decreased (26).

The effect of the particle size of DPC 963 (API) on the characteristics of granules prepared by high-shear wet granulation was evaluated by Badawy et al. (27). Particle agglomeration was affected by the particle size of the drug substance. Granule geometric mean diameter and fraction with particle size greater than

504

250 μm was inversely proportional to the particle size of the drug substance. The granules prepared with the smaller particle size had higher porosity, thus suggesting lower tendency for granule densification than those manufactured with the larger particle size. The compressibility of the granules was increased with decreasing particle size of the drug substance. The effect of particle size on granulation growth is the result of increased densification propensity from increased drug particle size.

In another study, a high-shear mixer granulator was used for pelletizing a drug. High-dose pseudoephedrine-HCl pellets were produced with MCC in a high-shear mixer granulator (28). The drug loading and drug particle size influenced the bulk and true densities of the resulting pellets.

5.3. Effects of Type and Amount of Binder Solution Used

A binder is normally required for the wet-granulation process. The binder can be added into the powder mixture as a dry powder followed by the addition of water, or an appropriate solvent to activate binding. Alternatively, the binder can also be added into the powder mixture as a binder solution. Because of the higher densification of the wet agglomerates, the high-shear granulation process normally only needs two-thirds to three-quarters of the liquid required during the low-shear granulation process (18). The bonding characteristics of the binders used for wet granulation could vary due to the differences in their physicochemical properties. Therefore, the type of binder used for granulation can influence the granulation process, the amount of binder required for granulation, and the physical properties of the obtained granules.

For example, the effect of binder solutions on the size of DCP granules was investigated by Ritala et al. (29). Five different binders, PVP (Kollidone 90), polyvinylpyrrolidone-polyvinylacetate copolymer (PVP-PVA copolymer), hydrolyzed gelatin and HPMC (Methocel E5 and Methocel E15) were studied. The granules prepared with PVP and hydrolyzed gelatin possessed a larger mean particle size and lower intragranular porosity when the same volume of binder solutions was used. The other three binder solutions behaved similarly. This could be due to the higher densification of DCP granule caused by PVP and hydrolyzed gelatin. Thus, the granules had higher liquid saturation with lower volumes of the binder solutions. It was apparent that increasing the concentration of the binder solution in the powder mixture increased the mean granule size.

In another study, Ritala et al. (30) investigated the differences between five binders during wet granulation using a high-shear granulator. The binders used for the study were PVP K90, PVP K25, PVP-PVA copolymer, Methocel E5, and Methocel E15. The results demonstrated that the binder solutions with high surface tension, such as PVP solutions, produced denser granules with larger mean particle size than those with low surface tension, such as PVP-PVA copolymer, Methocel E5, and Methocel E15. The difference of granule growth by different binders in high-shear wet granulation could be due to the variation of surface tension of the binder solutions.

The amount of binder and granulating liquid used during granulation affect the granulation process and the physical characteristics of the prepared granules. In general, the granules are finer when the amount of granulating liquid used for granulation is decreased. For example, the size of the granules prepared from three tablet excipients, lactose, glucose, and mannitol, increased when the amount of granulation liquid was increased (24). Similar results were observed for granulating

mixtures of mannitol and MCC (31). When the mixtures were granulated in a high-shear mixer using HPC as the binder, the mean particle size of the granules increased with increasing amounts of water and concentration of the binder.

Generally, an increase in binder concentration could result in the production of larger granules. However, this is not always the case with starch paste since it could behave differently from the other binders. For example, a high-shear mixer was utilized for evaluation of pregelatinized and pregelatinized, cross-linked, waxy corn starches as binding agents in the wet-granulation process (3). Increasing the concentration of the binders decreased the average granule size; however, no difference in friability of the granules was observed. The use of pregelatinized or pregelatinized, cross-linked starches as a paste provided larger and less friable granules than when the binder was added in the dry form.

The effect of starch paste concentrations on the particle size distribution of fine granules, produced by high-speed mixer, was investigated by Makino (32). When a low concentration (5%) of starch paste was used, the growth of granules occurred mainly during the massing time, since a relatively large amount of free water was available from the paste. Only the mean particle size of the granules became larger without changing the particle size distribution of the granules during granulation. However, when a high concentration (15%) of starch paste was used, rapid deaggregation of granules occurred due to the applied shear force, following the formation of large granules, immediately after the addition of the starch paste. Deaggregation of these large agglomerates became predominant during the wet-massing stage, and hence, the size distribution of the granules became narrower. Longer massing time was also required when a high concentration (15%) of starch paste was used, since only a small amount of water exuded from the more concentrated starch paste during the agitation.

Besides the effect on the particle size of the granules, the amount of binder solution used in the wet-granulation process can also affect the content uniformity of the granules. The effects of the amount of binder solution on the content uniformity of the oily drug *n*-alpha-tocopheryl acetate (VE) in granules obtained by high-shear wet granulation was investigated by Kato et al. (33). When the amount of binder solution was below the amount of water required to reach the plastic limit (minimum amount of water required for the powder mixture to form a large agglomerate when kneaded), the content of VE was <50% in the fractionated fine granules, but was >200% in the fractionated large granules. Large variations were seen in the contents of VE even if the granulation time was extended up to 30 min. When the amount of binder solution was at or above the amount of water required to reach the plastic limit, less variation was observed in the content of VE throughout the granules, and the content of VE was fairly uniform.

In another study, the effect of the amount of water as the granulating liquid and HPC as a binder on the pharmaceutical properties of granules of two model drugs, ascorbic acid and ethenzamide, was investigated by Miyamoto et al. (34). The dependence of drug content uniformity of these two model drugs on the granule size was also investigated in this study. For a water-soluble drug, ascorbic acid, an appreciable dependence of drug content on granule size was not observed in model formulations. However, for a poorly water-soluble drug, ethenzamide, more drug was found in small-size granules (<75 µm). The drug content of ethenzamide in small-size granules decreased with increasing amounts of HPC and granulation liquid. These observations suggested that drug content uniformity is influenced

not only by drug solubility in the binder solution, but also by the amounts of granulating liquid and the type of the binder used.

Granule friability is also influenced by the binder concentration and the amount of granulating liquid added to the formulation during granulation. For a new API granulated with lactose and Avicel PH 101 using low-viscosity HPMC (Pharmcoat 603), increasing the binder concentration and the amount of water tended to produce higher wet-mass consistencies. Granule friability decreased with an increase in the binder level. An inverse relationship was observed between granule friability and the amount of water added to the formulation, especially at lower drug concentrations (35).

The binder can influence not only the physical properties of the granules, but also the performance of the finished tablets. For example, within a certain range of binder concentrations and granulating liquid, increasing the amount of binder or granulating liquid actually decreases the compressibility of the granules (26). In another study, the effect of different types of binders such as PVP K30, HPMC (Cellulose HP-M 603), maltodextrin (Lycatab DSH), pregelatinized starch (Lycatab PGS), and low substituted hydroxypropyl cellulose (L-HPC) (type LH 11) on the hardness of placebo and paracetamol tablets using high-shear granulation technique was compared by Becker et al. (36). The placebo granules comprised only lactose and MCC (Avicel PH 102). The binders were added at 2%, 6%, and 10% in the dry form and water was used as the granulating liquid. The median particle size increased with increasing binder concentrations from 2% to 6% except when L-HPC was used as the binder. The median particle size of the granules decreased with increasing binder concentrations from 2% to 6% when L-HPC was used as the binder. The granule strength, and the hardness (crushing strength and friability) of the resulting tablets increased with increasing binder concentrations. In the preparation of model tablets containing paracetamol, PVP K30 (6%) and Cellulose HP-M 603 (6%) turned out to be the binders of choice with respect to crushing strength of the finished tablets. Lycatab PGS, Lycatab DSH, and L-HPCC-LH 11 could not be used to produce paracetamol tablets that met the requirements.

The amount of granulating water can also affect the physical properties and compressibility of MCC, which is one of the most commonly used fillers. The mechanism of forming hard granules with MCC, using a high-shear mixer granulator, was investigated by Suzuki et al. (37). The hardness of the MCC granules increased with granulation time and the amount of water added. The specific surface area decreased during the granulation process. Crystallite size of cellulose decreased with granulation time and with increasing amounts of water added. MCC granules were strengthened with longer granulation time and greater amounts of water, thus resulting in a more intricate network due to the strong shear force of the impeller.

The effect of granulating water level on the physical-mechanical properties of MCC and silicified microcrystalline cellulose (SMCC) was investigated by Habib et al. (38). Granules containing either MCC or SMCC were prepared at different water levels using a high-shear mixer. The resulting granules were tray dried. The water level ranged from 0% to 100%. Increasing the water level affected the granule particle size, increased the granular density and flow properties of the granules, and decreased the porosity and compactibility. The compactibilities of both materials were similar and acceptable at each granulating water level up to 40%. However, both the materials showed poor compactibility at higher water levels. The effect of amount of water used for granulation did not have a statistically significant difference on the compressibility of MCC and SMCC. SMCC did not offer practical advantages over MCC, other than better flow in the powder form, which could be

507

agent and it must be present at an optimal concentration to maximize the solubility of a poorly water-soluble drug. Table 4 lists some of the common solubilizing agents. One commonly used additive is cyclodextrin. Cyclodextrins are bucket-shaped oligosaccharides produced from starch.

As a result of their molecular structures and shapes, cyclodextrins are able to entrap poorly water-soluble drugs in the hydrophobic cavities forming water-soluble inclusion complexes with the poorly water-soluble drugs. Cavallari et al. (30) showed that complexation and granulation of piroxicam with β -cyclodextrin by steam granulation in a single process improved in vitro drug release when compared to a physical mixture of drug and β -cyclodextrin in the same composition. 2-Hydroxypropyl- β -cyclodextrin was employed by Uekama et al. (31) to form water-soluble inclusion complex with nifedipine. The drug and additive were dissolved in ethanol-dichloromethane and subsequently spray dried. Tablets prepared using the inclusion complexes were found to promote nifedipine in vitro release rate. Upon feeding the test tablets to dogs, superior oral bioavailability was obtained. Storage at 60°C and 75% relative humidity did not result in nifedipine crystal growth because the nifedipine molecules were basically entrapped within the 2-hydroxypropyl- β -cyclodextrin, minimizing the opportunity for the nifedipine molecules coming together and recrystallizing. Thus, the stability in dissolution profile could be achieved throughout the entire period of study.

2.2.2. Effervescent Agent

Effervescence is defined as the evolution of bubbles of gas from a liquid as the result of a chemical reaction. The generation of gas, which is usually carbon dioxide, is usually achieved by spontaneous chemical reaction between a soluble acid source and an alkali metal carbonate in the presence of water. The reaction can be triggered in the presence of a small amount of water, thus moisture protection of such oral dosage forms is paramount. This is because effervescence reaction when initiated will proceed spontaneously because one of the by-products is water.

Several researchers had found that the bioavailability of aspirin from effervescence tablet was higher than conventional or enteric-coated tablets (32-34). The reasons for this included the dramatic disintegration rate of the tablets that enabled rapid release of the drug particles for dissolution and the increase in gastric emptying rate.

2.2.3. Hydrophilic Agent

In the formulation of rapid release granules, it is important to consider the formulation in its totality. It is always better to employ more hydrophilic agents which may be water-soluble or water-insoluble as binders or fillers in the formulation so that water penetration into the granules will not be impeded. Hydrophilic agents commonly employed include hydroxylpropylcellulose, hydropropylmethylcellulose, lactose, microcrystalline cellulose, polyvinylpyrrolidone, starch, and many others. These additives aid in wetting the poorly water-soluble drug. Polyvinylpyrrolidone K30 was able to improve the wetting of nifedipine complexed with 2-hydroxypropyl- β -cyclodextrin, thus negating the decrease in nifedipine release brought about by the poor wettability and good compressibility of the complex (35).

19

Bioavailability and Granule Properties

Sunil S. Jambhekar

South University School of Pharmacy, Savannah, Georgia, U.S.A.

1. INTRODUCTION

The most important property of a dosage form is its ability to deliver the active ingredient to the "site of action" in an amount sufficient to elicit the desired pharmacological response. This property of a dosage form has been variously referred to as its physiological availability, biological availability, or bioavailability.

Bioavailability may be defined more accurately as the rate and extent of absorption of a drug from its dosage form into the systemic circulation. Accordingly, the absorption of a drug following intravenous administration is extremely rapid and complete. However, due to convenience and stability problems, drugs are often administered orally in a tablet or capsule dosage form. Therefore, it is imperative that their rate and extent of absorption in individual be known accurately. Furthermore, it is equally important that the factors that influence the rate and extent of absorption of drugs be also known and understood by formulators.

The subject of bioavailability began to receive growing attention as studies showed that the therapeutic effectiveness of a drug from the dosage form depends, to a large extent, on the physiological availability of their active ingredient(s), and is a function of the drug concentration in the patient's blood or plasma. The importance of bioavailability in drug therapy, therefore, stems from the fact that the rate and extent of absorption of a drug from a dosage form can, in fact, affect the patient's response to a drug. In light of these facts, the determination of bioavailability has become one of the ways to assess the in vivo performance of a dosage form following its formulation development. It must, however, be remembered that bioavailability studies, very often, are conducted in normal, fasted, and a small number of subjects and, therefore, the results of these studies may not always reflect the true efficacy relationship in patients under treatment conditions.

For many years it was assumed that if a dosage form contained the labeled amount of a drug, its performance could be taken for granted. However, it is now evident for some time that many factors acting individually or in concert may produce the therapeutic failure.

509

2. BIOAVAILABILITY PARAMETERS

In assessing the bioavailability of a drug from a dosage form, three parameters are measured following the administration of a drug through a dosage form and obtaining the drug blood concentration time profile (Fig. 1):

1. Peak concentration (C_p)_{max}
2. Peak time, t_{max}
3. The area under the concentration time curve, $(AUC)_0^\infty$

The parameters t_{max} and $(C_p)_{max}$ are the measure of the rate of absorption and the $(AUC)_0^\infty$ is a measure of the extent of absorption.

2.1. Peak Time

This parameter represents the length of time required to attain the maximum concentration of drug in the systemic circulation. The parameter reflects the onset of action and, hence, can be utilized as a measure of the rate of absorption. The faster the rate of absorption, the smaller the value for the peak time and the quicker the onset of action of the drug. The peak time is determined by using the following equation:

$$t_{max} = \frac{\ln(K_a/K)}{(K_a - K)} \quad (2.1)$$

where K_a and K are the first-order absorption and elimination rate constants, respectively.

Eq. 2.1 clearly indicates that larger the value of the absorption rate constant (K_a), the smaller is the value of peak time (t_{max}) and the quicker is likely to be the onset of action.

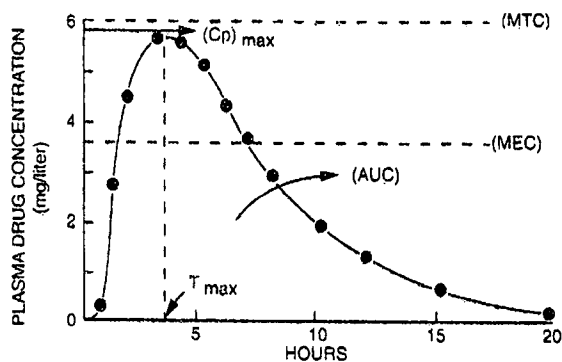


Figure 1 A graphical representation of plasma/serum drug concentration data following the administration of a drug by an extravascular route.

542

The elimination rate constant (K) is constant for a drug in normal healthy individuals and it changes when organs responsible for the elimination of the drug (i.e., kidney and liver) exhibit abnormalities. The absorption rate constant (K_a), on the other hand, depends on the route of administration, the dosage form, and the formulation of a drug. And, for hydrophobic drugs or when the absorption is dissolution rate limited, the faster dissolution is generally reflected in the higher value for the absorption rate constant. Therefore, by changing the formulation of a drug or route of administration, one can alter the peak time and, therefore, the rate of absorption and time for the onset of action.

2.2. Peak Plasma Concentration (C_p)_{max}

This parameter represents the highest drug concentration in the systemic circulation or the plasma concentration that corresponds to the peak time. Furthermore, this parameter is often associated with the intensity of the pharmacologic response of the drug. Therefore, the peak plasma concentration (Fig. 1) of a drug following the administration of a dosage form should be above the minimum effective concentration and below the minimum toxic concentration. The peak plasma concentration can depend on the absorption rate constant (K_a) and the fraction of the administered dose that eventually reaches the systemic circulation. The higher the absorption rate constant and fraction that reaches the general circulation, the greater is the peak plasma concentration for the administered dose. The route of administration, the dosage form, and the formulation can therefore influence the peak plasma concentration. It is determined by using the following method:

$$(C_p)_{\max} = \frac{K_a F (X_a)_0}{V(K_a - K)} (e^{-K t_{\max}} - e^{-K_a t_{\max}}) \quad (2.2)$$

where F is the fraction of the dose that eventually reaches the systemic circulation, $(X_a)_0$ is the administered dose, V is the apparent volume of distribution of a drug, and $t_{\max}$ is the peak time.

Since the term $(K_a F (X_a)_0) / (V(K_a - K))$ in Eq. 2.2 constitutes the intercept of the plasma concentrations against the time profile, Eq. 2.3 can be written as

$$(C_p)_{\max} = I (e^{-K t_{\max}} - e^{-K_a t_{\max}}) \quad (2.3)$$

where I is the intercept ($\mu\text{g/mL}$) of the plasma concentrations against time profile.

2.3. Area under the Plasma Concentration Time Curve

This parameter represents the extent of absorption of a drug following the administration of a dosage form. The greater the fraction of the dose that reaches the general circulation the greater is the extent of the absorption and, hence, $(AUC)_0^\infty$. The term $(AUC)_0^\infty$, expressed as $\mu\text{g/mL/hr}$, for a drug following its administration by various extravascular routes or various dosage forms that are administered extravascularly, is determined by employing the following equation:

$$(AUC)_0^\infty = \frac{K_a F (X_a)_0}{V(K_a - K)} \left[\frac{1}{K} - \frac{1}{K_a} \right] \quad (2.4)$$

All the terms of the Eq. 2.4 have been defined previously. Eq. 2.4 can further be reduced to

57A

$$(AUC)_0^\infty = \text{Intercept} \left[\frac{1}{K} - \frac{1}{K_a} \right] \quad (2.5)$$

the intercept in Eq. 2.5 being the intercept of the plasma concentration time profile. The extent of absorption can also be determined by using the following equation:

$$(AUC)_0^\infty = \frac{F(X_a)_0}{VK} \quad (2.6)$$

where, the term VK is the systemic clearance of the administered drug. This parameter being independent of the route of administration, the formulation, and the extravascularly administered dosage form, it is ostensible that the extent of absorption [i.e., $(AUC)_0^\infty$] is controlled by the product of the fraction of the administered dose reaching the general circulation and the administered dose [i.e., $F(X_a)_0$].

2.4. Factors Affecting the Bioavailability

There are a number of factors responsible for the variation in bioavailability. Broadly speaking, these factors can be classified as patient related or dosage form related. Patient related factors include age, disease state, abnormal genetic characteristics, and gastrointestinal physiology. The detailed discussion on these factors is beyond the scope of the objectives of this chapter.

Dosage form related factors include formulation and manufacturing related variables such as particle size, type, and quantity of excipient used, method of manufacturing, compression pressure, derived properties of the powder, and many other factors.

The fact that the bioavailability of a drug may be significantly affected by its physical state of the drug and the dosage forms via which it is administered has been unequivocally demonstrated. And, because drugs are administered through dosage forms, these dosage forms should have adequate stability, consistent bioavailability, and uniform composition.

Following the administration of a drug through a solid dosage form, a sequence of steps are required before the drug reaches the systemic circulation. As shown in Figure 2, an orally administered solid dosage form undergoes disintegration and deaggregation, followed by the dissolution of the drug. The dissolved drug molecules must penetrate the gastrointestinal membrane and picked up by the blood. Each of the steps involved may limit how fast the drug molecules reach the general circulation and, therefore, site of action. The step that offers the maximum resistance is referred to as the rate-limiting step. Which step will be rate limiting, on the other hand, will depend on the physicochemical properties of the dosage form and the physiology of the gastrointestinal tract. The focus of the discussion here, however, will be on the physicochemical properties of the dosage form.

As illustrated in Figure 2, solid dosage form must disintegrate or deaggregate before much of the drug is available for absorption. Drug dissolution subsequently occurs from the resulting granules. Therefore, the properties of granules are important in understanding how dissolution is influenced by these properties. Following the ingestion of a solid dosage form, whether or not a drug is deaggregated, it will not be absorbed until it has dissolved into the luminal fluids of the gastrointestinal tract. Because of the effects of disintegration and deaggregation on the dissolution, the remaining discussion will focus on the factors influencing the dissolution of the drug.

SOS
SAC

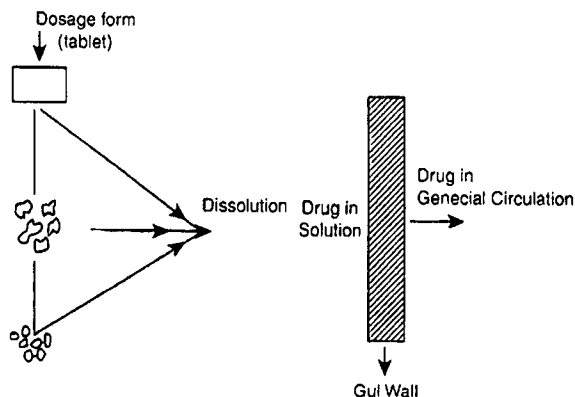


Figure 2 Schematic representation of the process of the drug dissolution and its entry into the general circulation.

2.5. Dissolution and Granule Properties

Amongst available dosage forms, compressed tablets are the most widely used dosage form. Tablets are generally obtained by using either wet granulation or direct compression process. Wet granulation process consists of mixing a drug with other powdered material and wetting the mixture with an aqueous or hydroalcoholic solution of a suitable binder such as gelatin, starch, or polyvinylpyrrolidone. The damp mass is passed through the screens of 8–12 mesh and dried to produce cohesive granules. Each granule, in theory, is a blend of an active ingredient and excipients. The granules flow easily through the hopper into the tablet press and are easily compressed.

Many derived properties of the powder greatly influence the granule properties, which, in turn, influence the dissolution of an active ingredient from the dosage form. These derived properties include powder density, porosity, specific surface, particle number, and powder flow. These derived properties are, in essence, determined by the particle size and size distribution. Consequently, particle size and size distribution play a vital role in influencing the bioavailability of drugs, particularly, when dissolution is the rate-limiting step in the absorption process. The important role these properties play in influencing the bioavailability must, therefore, be recognized and taken into consideration during optimization of a dosage form formulation. For example, a smaller particle size is desirable, if the drug is hydrophobic, to improve the drug dissolution due to increased specific surface; however, too small a particle size may adversely affect the powder flow and content uniformity of a dosage form. Other derived powder properties like true and bulk density and particle size will play an important role in the mixing of powder blends, prior to granulation and compression. Powder flow is another derived property of importance. Flow of the powder and granules can present difficulties in the manufacturing of a tablet

509
1512

dosage form, which, in turn, can affect the content uniformity of a drug and the bioavailability.

Many processes used in the tablet manufacturing greatly influence the dissolution rates of the active ingredient. The method of manufacture, the size, the moisture content, age and the flow property of the granules, the order of mixing of ingredients during the granulation, as well as the compression force employed in the tableting process, all contribute to the dissolution characteristics of the final product and, therefore, may be the bioavailability of a drug from the finished product.

Several studies have demonstrated that the granulation process, in general, enhances the dissolution rate of poorly soluble drugs (1). The use of diluents and fillers such as starch (2), anhydrous (3) and spray dried lactose (4,5), microcrystalline cellulose (6), and compression force, particle size and lubricants (7) tends to enhance the hydrophilicity of the active ingredients and improve their dissolution characteristics. In this regard, the wet granulation procedure was considered a superior method compared to other methods. However, newer tableting machines and excipients, accompanied by careful formulation and proper mixing sequence, will permit preparation of tablets with good dissolution characteristics and not dictated by the method of preparation per se.

Marlow and Shangraw (8) reported that sodium salicylate tablets prepared by direct compression with spray dried lactose uniformly exhibited more rapid and complete dissolution compared to those prepared by wet granulation. Furthermore, it was reported that the presence of disintegrate in the dry compression was essential for good dissolution. Finholt et al. (9) reported, in a separate comparative study, utilizing phenobarbital tablets that were manufactured by both wet and dry granulation that both procedures yielded comparable dissolution rates provided a disintegrate was incorporated and mixed with drug before dry granulation. However, the incorporation of disintegrate following the dry granulation of a drug resulted in slower dissolution rates.

In the manufacturing of tablets by the conventional wet granulation method, there are many independent factors that affect the property of granules and, therefore, the dissolution rate. Recent advances in granulation technology and the employment of high-shear mixers and fluid bed granulating equipment have helped to identify several critical in-process variables. The systematic control of variables such as the type and time of mixing of the granules, time and temperature of drying, blending time with lubricant, age of the granules, moisture content of the granules at the time of compression, and the tablet crushing strength are of importance to ensure the consistency in the dissolution and, hence, bioavailability.

In early studies on the physics of tablet compression, Higuchi et al. (10) recognized the influence of compressional forces employed in the tableting process on the apparent density, porosity, hardness, disintegration time, and average particle size of the compressed tablets. Hardness is a measure of resistance of a dosage form to the mechanical deforming. It is a function of high compression forces used in the manufacturing, and it may change with the aging of granules. Higuchi et al. (10) reported a linear relationship between hardness and the logarithm of the compressional force, and the specific surface of the compressed tablets was found to undergo marked changes during the compressional process. The high compression may increase the specific surface and, hence, may enhance the dissolution. On the other hand, the high compression may also inhibit the wettability of a tablet due to the formation of a firmer and more effective sealing layer of the lubricant due to high pressure and temperature that accompany a strong compressional force. Levy et al. (2) reported

574

that salicylic acid tablets, when prepared by double compression, showed an increase in the dissolution with an increase in the pre-compression pressure due to fracturing of drug particles at higher pressure. The higher compression may also produce slower dissolution, at least in the initial period, due to an increased difficulty of fluid penetration into the compressed tablets. Luzzi et al. (11) and Jalsenjak (12) observed the dissolution rate of sodium phenobarbital to be inversely proportional to the hardness from tablet and microcapsule, respectively.

Another important granule property that influences the dissolution of drug is the moisture content of the granule at the time of compression. Chowhan et al. (13-17) studied the effect of moisture content and crushing strength on ticlopidine hydrochloride tablet friability and dissolution. It was observed (16) that at the moisture content of 1-2%, the drug dissolution was inversely related to the tablet crushing strength. However, at the moisture content level of 3-4%, there was no clear relationship between the dissolution and the crushing strength.

In later studies by Chowhan et al. (14,17), it was reported that the granules prepared by high-speed shear mixer were less porous than those prepared by planetary mixer, and the porosity of the tablet may improve the dissolution of drug by facilitating solvent penetration provided the entrapment of air in the pores is minimized or avoided.

In yet another important study, Levy et al. (2) studied the effect of the granule size on the dissolution rate of salicylic acid tablets and found that the dissolution rate increased with a decrease in the granule size; the increase in dissolution rate, however, was not proportional to the increase in the apparent surface area of the granules. Furthermore, it was also reported that the dissolution rate decreased significantly with the increase in the age of the granules.

The chemical components of the formulation have also been shown to prolong disintegration time, which subsequently affect the drug dissolution and bioavailability. Inert fillers have been found to potentiate the chemical degradation of active ingredient causing alteration in the disintegration and dissolution time of compressed tablets to change with storage. Alam and Parrott (18) have shown that hydrochlorothiazide tablets, granulated with acacia and stored at temperatures ranging from room temperature to 80°C increased in hardness with time. This was reflected in increased disintegration and dissolution time. On the other hand, tablets granulated with starch and polyvinylpyrrolidone did not show any change in disintegration and dissolution time.

3. CONCLUSION

Drug availability following the oral dosing may be thought of as the result of the following steps:

1. Getting the drug into solution.
2. Moving the drug molecules through the membrane of the gastrointestinal tract.
3. Moving the drug away from the site of administration into the general circulation.

It is clear from the discussion that the bioavailability of drugs, particularly poorly soluble drugs, mainly depends on the ability of the drug to dissolve at the site of administration. The dissolution, in turn, especially from solid dosage forms such

JSA

as tablet and capsule, depends on the powder properties, granule properties, and the processing variables used in the manufacture of the dosage forms. The granule properties and other variables, which determine and influence the granule properties, will serve as major topics of discussion in subsequent chapters. Knowledge of these factors and their role in influencing the bioavailability of a drug will allow the formulators to develop an optimum drug dosage form by selecting the process and preparation variables involved in a rational manner.

REFERENCES

1. Solvang S, Finholt P. Effect of tablet processing and formulation factors on dissolution rates of active ingredient in human gastric juice. *J Pharm Sci* 1970; 59:49-52.
2. Levy G, Antkowiak J, Procknal J, White D. Effect of certain tablet formulation factors on dissolution rate of the active ingredient II: granule size, starch concentration, and compression pressure. *J Pharm Sci* 1963; 52:1047-1051.
3. Batuyios N. Anhydrous lactose in direct tablet compression. *J Pharm Sci* 1966; 55: 727-730.
4. Gunsel W, Lachman L. Comparative evaluation of tablet formulations prepared by conventionally processed and spray dried lactose. *J Pharm Sci* 1963; 52:178-182.
5. Duvall R, Koshy K, Dashiell R. Comparative evaluation of dextrose and spray dried lactose in direct compression systems. *J Pharm Sci* 1965; 54:1196-1200.
6. Reier G, Shangraw R. Microcrystalline cellulose in tableting. *J Pharm Sci* 1966; 55: 510-514.
7. Iranloye T, Parrott E. Compression force, particle size, and lubricants on dissolution rates. *J Pharm Sci* 1978; 67:535-539.
8. Marlow E, Shangraw R. Dissolution of sodium salicylate from tablet matrices prepared by wet granulation and direct compression. *J Pharm Sci* 1967; 56:498-504.
9. Finholt P, Pedersen P, Solvang R, Wold K. *Mødd Norsk Farm Selsk* 1966; 28:238.
10. Higuchi T, Rao A, Busse E, Swintosky J. The physics of tablet compression II: the influence of degree of compression on properties of tablets. *Am Pharm Assoc Sci Ed* 1953; 42:194-200.
11. Luzzi L, Zoglio M, Maulding H. Preparation and evaluation of the prolonged release properties of nylon microcapsules. *J Pharm Sci* 1970; 59:338-341.
12. Jalsenjak I, Nicolaidou C, Nixon J. Dissolution from tablets prepared using ethylcellulose microspheres. *J Pharm Pharmacol* 1977; 29:169-172.
13. Chowhan ZT, Palagyi L. Hardness increase induced by partial moisture loss in compressed tablets and its effect on in vitro dissolution. *J Pharm Sci* 1978; 67:1385-1389.
14. Chowhan ZT. Moisture, hardness, disintegration and dissolution interrelationships in compressed tablets prepared by the wet granulation process. *Drug Dev Ind Pharm* 1979; 5(1):41-62.
15. Chowhan ZT. Role of binders in moisture-induced hardness increase in compressed tablets and its effect on in vitro disintegration and dissolution. *J Pharm Sci* 1980; 69:1-4.
16. Chowhan Z, Yang I, Amaro A, Chi L. Effect of moisture and crushing strength on tablet friability and in vitro dissolution. *J Pharm Sci* 1982; 71:1371-1375.
17. Chowhan Z, Chatterjee B. A method for establishing in process variable controls for optimizing tablet friability and in vitro dissolution. *Int J Pharm Technol Prod Manuf* 1984; 5(2):6-12.
18. Alam AS, Parrott EL. Effect of aging on some physical properties of hydrochlorothiazide tablets. *J Pharm Sci* 1971; 60:263-266.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -



Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 129698

Bogotá D.C., Diciembre 05 de 2014 - 09:36:35

RECIBIDO DE : OLARTE MOURE & ASOCIADOS

NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	705420693	04/12/2014	10.630.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNIDITARIO	Vr. CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICACIONES	EN CREACION CORRECCION A SOLICITUD EN TRAMITE / MODIFICA	128.000.00	128.000.00
				\$128.000.00

SON: **CIENTO VEINTIOCHO MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-101248- -00009-0000

Fecha: 2014-12-05 16:45:00 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 412 REPOSPRESRECU Folios: 35

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

, Diciembre 5 de 2014 - 09:36:39

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 130213

Bogotá D.C., Diciembre 05 de 2014 - 16:22:38

RECIBIDO DE : OLARTE MOURE & ASOCIADOS

NI 830.122.870

RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
RECIBO DE CA	999999999	129678	05/12/2014		62.000.00
RECIBO DE CA	999999999	129681	05/12/2014		217.000.00

*** Conceptos Pagados ***

CANT. RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
8 50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	31.000.00	248.000.00
			\$248.000.00

SON: **DOSCIENTOS CUARENTA Y OCHO MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-101248- -00009-0000

Fecha: 2014-12-05 16:45:00 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 412 REPOSPRESRECU Folios: 35

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Diciembre 5 de 2014 - 16:22:38